SKIN CANCER (OTHER THAN MELANOMA)

SKIN MICROENVIRONMENT ENHANCES PROLIFERATION INDEX AND ACTIVATES PI3K/AKT/MTORC1 PATHWAY IN SEZARY SYNDROME

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Introduction: Sézary Syndrome (SS) is a rare and aggressive variant of Cutaneous-T-Cell Lymphoma characterized by distribution of neoplastic lymphocytes (the SS cells) mainly in blood, skin and lymph-node. As the role of skin in SS pathogenesis is still unclear, we compared skin and blood-derived SS cells concurrently obtained from SS patients highlighting a greater proliferation index (PI) and PI3K/AKT/mTORC1 activation level in skin derived SS cells. We also analyzed this pathway at genomic and biochemical level in SS cell lines and primary tumor cells.

Objective: Elucidate the role of PI3K/AKT/mTORC1 pathway through the interaction in-vivo of skin-SS cells

Materials and Methods: PI was measured by Ki67 expression detected in matched-blood samples and skin-paraffin biopsies by flow cytometry analysis and immunohistochemistry. Phosphorylation levels of members of PI3k/AKT/mTOR pathway were assessed in matched blood/skin samples using an AKT kinase array. mTORC1 signaling activation was evaluated by WB. Cell proliferation was measured by MTT assay. Copy number variation (CNV) of members of PI3K/AKT/mTORC1 pathway was evaluated by Affymetrix SNP6.0 arrays in a cohort of 63 SS samples (43 patients plus 20 Follow up). CNV and survival were correlated by Kaplan Meier (KM) analysis.

Results: Skin derived SS cells showed a greater PI (Fold change (FC) 5.8; P=0.01) and PI3K/AKT/mTORC1 activation level, particularly of mTOR protein (FC from3.9 to 22.9) respect to paired-blood-SS cells. SDF-1 and CCL21 chemokines, both overexpressed in skin lesions, significantly induce mTORC1 activation and cell proliferation in SS cells We

observed recurrent CNVs, namely: loss of LKB1 (48%), PTEN (39%) and PDCD4 (35%) and gains of P70S6K (30%). The CNV of PTEN, PDCD4 and P70S6K, were associated to a reduced survival of SS patients (P≤0.05).

Conclusion: Skin microenvironment promotes the PI and PI3K/AKT/mTORC1 activation, a pathway with recurrent genomic alterations that correlate with SS prognosis